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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,477	03/18/2005	Christopher Luckhurst	06275-448US1	8642

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EXAMINER

O DELL, DAVID K

ART UNIT	PAPER NUMBER
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1625

NOTIFICATION DATE	DELIVERY MODE
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02/24/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No. 10/528,477	Applicant(s) LUCKHURST ET AL.	
	Examiner David K. O'Dell	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-6,8,9 and 12 is/are pending in the application.
- 4a) Of the above claim(s) 8, 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-6 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This application is a 371 of PCT/SE03/01425 filed 09/12/2003 and claims priority to Swedish application 0202838-9 filed 09/24/2002.

Claims 1-2, 4-6, 8-9, 12 are pending. Claims 8 & 12 are withdrawn. Claim 8 was previously listed in the FINAL rejection of August 26, 2008 as rejected, however this claim was not examined on the merits and was inadvertently included in the rejections. The examiner apologizes for any confusion. Confusion sometimes arises when product and process claims are not grouped together See MPEP 608.01(m) Form of Claims:

“Claims should preferably be arranged in order of scope so that the first claim presented is the least restrictive. All dependent claims should be grouped together with the claim or claims to which they refer to the extent practicable. Where separate species are claimed, the claims of like species should be grouped together where possible. **Similarly, product and process claims should be separately grouped. Such arrangements are for the purpose of facilitating classification and examination.**”

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 17, 2008 has been entered.

Claim Rejections withdrawn

3. The rejection of claims 1-2, 4-6, 9, under 35 U.S.C. 103(a) as being unpatentable over Lawrence, et. al. WO 2001077101 A1 (cited on the IDS) in view of Ko et. al. WO 200035877 (cited on the IDS) is withdrawn, based on the amendments. The double patenting rejection over

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7,179,922 is withdrawn since the Z moiety distinguishes the instant claims from those of the '922 patent.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

4. Upon further consideration, a new ground(s) of rejection is made in view of a reappraisal of the state of the art at the applicant's representative's behest. The rejection over 10/508,331 is maintained for the reasons of record since position isomers are in fact *prima facie* obvious. The teaching of Ko is used to substantiate this finding, but it is not necessary. It is routine for a chemist to make position isomers.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 4-6, 9, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, which have at least one member of the Markush genus exemplified, it does not reasonably provide enablement for the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

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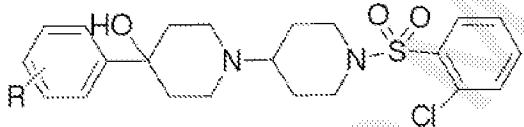
- (A) *The breadth of the claims;*
- (B) *The nature of the invention;*
- (C) *The state of the prior art;*
- (D) *The level of one of ordinary skill;*
- (E) *The level of predictability in the art;*
- (F) *The amount of direction provided by the inventor;*
- (G) *The existence of working examples; and*
- (H) *The quantity of experimentation needed to make or use the invention*

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should be active as chemokine receptor antagonists. **(D) The level of one of ordinary skill:** One of ordinary skill is a practicing organic chemist/medicinal. **(C) The state of the prior art:** **(E) The level of predictability in the art:** **(F) The amount of direction provided by the inventor,** **(G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. These compounds are sensitive to structural changes that may be relatively minor in the chemical sense, see Xie, et. al. "Identification of novel series of human CCR1 antagonists," *Bioorganic & Medicinal Chemistry Letters* **2008**, 18, 2215–2221.

"Compound **63**, where the positions of the halogens were switched, retained comparable potency (**63** vs. **61**) suggesting the importance of 4-halogen on the phenyl ring. By contrast, replacement of the 4-chloro with the bulky tBu (**65**) and phenyl (**66**) groups resulted in total loss of affinity, suggesting a space restriction around this site. All other substituents (for example, OMe, SMe and OPh) led to inactive compounds."

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Table 6. SAR of substitution on the left aromatic in the 1, 4'-bipiperidin-4-ol linker series


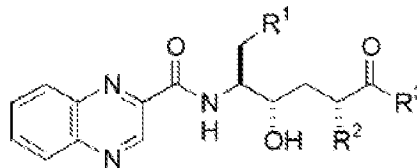
Compound	R	CCR1 binding ^a IC ₅₀ , μM	Ca ²⁺ flux ^b IC ₅₀ , μM
65	4-tBu	>10	>10
66	4-Ph	>10	>10
67	4-OMe	>10	>10
68	4-SMe	>10	7.98

In fact many substituents are not tolerated at all, resulting in “a total loss of affinity.” (C) (E)

As further of evidence of the extreme unpredictability in the chemokine antagonist development art see Brown et. al. “Novel CCR1 antagonists with improved metabolic stability”



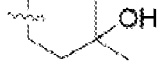
Bioorganic & Medicinal Chemistry Letters **2004**, 14, 2175–2179:

“Exploration of the C-5 position revealed that a number of halobenzyl C-5 substituents imparted a significant improvement in potency. Most notably, the 3-fluorobenzyl analogue 6j was shown to be >10-fold more potent than the desfluoro analogue 6b and also retained excellent HLM stability. Interestingly, the SAR in this region of the molecule was quite sensitive to minor structural changes. For example, while the 3-fluorobenzyl analogue 6j showed good potency, the closely related 4-fluorobenzyl analogue 6k was inactive.”



Compound	R ¹	R ²	R ³	CCL3 binding IC ₅₀ (μM)	CCL3 chemo- taxis IC ₅₀ (μM)
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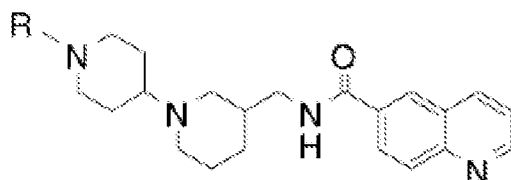
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6i	2-Fluorophenyl		-NH ₂	0.052	0.68
6j	3-Fluorophenyl		-NH ₂	0.046	0.065
6k	4-Fluorophenyl		-NH ₂	>25	>25

Here it is very clearly shown that what appears to a relatively innocuous change results in compounds with no activity. (C) (E)

CCR3 activity is also highly dependent upon the structure of the compound in particular N-Benzyl piperdines are well-known to have limitations on the substituents on the phenyl ring, see Ting et. al. "The synthesis of substituted bipiperidine amide compounds as CCR3 ligands: Antagonists versus agonists" *Bioorganic & Medicinal Chemistry Letters* **2005** 15, 3020–3023:

"The monosubstituted 2-chloro analogue 11c is inactive while the 4-chloro analogue 11d shows reasonable CCR3 affinity. The saturated cyclohexylmethyl analogue 11e is completely inactive. Methyl substitution at the benzylic position as in 11f or extension to the 3,4-dichlorophenethyl as in 11g also decrease affinity. Replacement of the 3,4-dichlorobenzyl moiety with the corresponding amide moieties as in compounds 11h and 11i or the urea moiety as in compound 11j also produces inactive analogues."

Table 2. In vitro CCR3 membrane binding and agonist (GTP γ S) activity of benzyl piperidine analogues **4i** and **11a-j**

Compd	R	K_i (nM)	E_{\max} % GTP γ S ^a
4i	3,4-DiCl-PhCH ₂	23 \pm 1	—7
11a	3,5-DiCl-PhCH ₂	398 \pm 59	45
11b	2,5-DiCl-PhCH ₂	391 \pm 44	45
11c	2-Cl-PhCH ₂	36% ^a	NT
11d	4-Cl-PhCH ₂	95 \pm 7	—8
11e	CyclohexylCH ₂	17% ^b	NT
11f	3,4-DiCl-PhCHMe	74 \pm 3	—12
11g	3,4-DiCl-PhCH ₂ CH ₂	180 \pm 32	2
11h	3,4-DiCl-PhCO	20% ^b	NT
11i	3,4-DiCl-PhCH ₂ CO	767 \pm 16	NT
11j	3,4-DiCl-PhNHCONH	6% ^b	NT

NT = not tested.

^a E_{\max} % at 10 μ M (n = 2).

^b % inhibition at 1 μ M (n = 2).

It is quite notable that all the compounds of the instant case have a dichlorophenyl moiety in the position corresponding to the R of Table 2 of Ting.

For CCR5 ligands many limitations are well known in the art. In a study of similar compounds Thoma, et. al. “Orally Bioavailable Competitive CCR5 Antagonists” *Journal of Medicinal Chemistry* **2004**, 47, 1939-1955, made the following statement, about substituents on the phenyl rings:

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“First we explored a few analogues of the highly potent CCR5 antagonist 1a with a cyano substituent in different positions of the benzyl group (Table 1). The 3-substituted compound 1c was found to be even more potent than unsubstituted 1a on both human and cyno CCR5. The 2-substituted derivative 1b was significantly less potent than 1a in the human binding assay but highly inferior in the Ca²⁺-mobilization assay. In addition, it was found to be almost inactive on cyno CCR5. The 4-substituted derivative 1d was considerably less potent than 1c. Compound 1e with a trimethoxybenzyl group was found to be completely inactive. These findings suggest that substituents of the benzyl group are well tolerated in the 3-position but can significantly reduce the affinity when attached to other ring positions. Furthermore, the substitution pattern seems to affect the reactivity on human vs cyno CCR5.” Pg. 1941 (C & E)

Thus it is clear that substitution can have a very pronounced impact on the active pharmacophore, and a choice of the wrong substituent or too many substituents gives compounds with no activity. The claims here may have many substituents most of which are prophetic. All the working examples have very limited substituents. The applicant's representative's remarks of May 12, 2008 admit to these facts, which are quoted here from page 15:

“Because the biological activity of a compound is highly dependent on the capability of being able to fit to specific chemokine receptors, such a modification would lead to significant changes in biological activity and may even lead to complete inactivation of the modified compound. Thus, such a modification would not be considered by one skilled in the art as a simple "optimization" of a biological compound.”

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the

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examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

We have been given no information in regard to the molecular determinants of chemokine inhibition for the compounds of the instant case. **(F & G)** The factors outlined in *In Re Wands* mentioned above apply here, and in particular as per the MPEP 2164.01 (a): “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” It is very clear that one could not make/use this very broad invention that has only two working examples in this unpredictable art without undue experimentation. **(C, E, F, G, H)**.

6. Claims 1-2, 4-6, 9, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. “The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue

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experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

a) Determining if any particular substrate would form a solvate or hydrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended. b) The direction concerning the hydrates is not found in the specification. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. The state of the solvate art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its

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Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula IIa as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Double Patenting

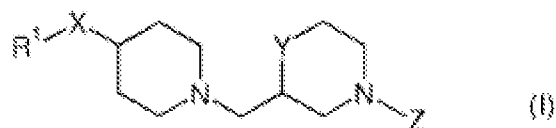
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-2, 4-6, 9, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,2, 4-7, 9-11 of copending Application No. 10/508,331 in view of Ko et. al. WO 200035877 (cited on the IDS). Although the conflicting claims are not identical, they are not patentably distinct from each other because the ‘331 application is drawn to position isomers of the elected species (and the generic claims as well). In claim 1 of the ‘331 application:

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wherein:

X is CH_2 , $\text{C}(\text{O})$, O , S , $\text{S}(\text{O})$, $\text{S}(\text{O})_2$ or NR^4 ;Y is O or CH_2 ; R^2 is

aryl or heterocyclyl

X is O ,Y is CH_2 ; R^3 is aryl

It is clear that the instant case is drawn to 4-piperidinyl compounds, while the '331 application is drawn towards 3-piperidinyl compounds. Ko teaches that the 3-piperidines have activity. Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds. This is exactly what has happened here. *In re JONES* 74 USPQ 152 (4-methyl naphthyl-1-acetic acid and 2-methyl naphthyl-1-acetic acid obvious over a reference teaching 1-methyl naphthyl-2-acetic

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acid), quoted with approval by *Ex parte MOWRY AND SEYMOUR* 91 USPQ 219, *Ex parte Ulliyot* 103 USPQ 185 (4-hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinoline obvious over a reference teaching 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline), "[p]osition isomers are recognized by chemists as similar materials", *Ex parte BIEL* 124 USPQ 109 (N-ethyl-3-piperidyl diphenylacetate obvious over a reference teaching N-alkyl-4-piperidyl diphenylacetate), "[appellant's arguments] do not, in any way, obviate the plain fact that appellant's DACTIL is an isomer of McElvain et al.'s compound. This close relationship places a burden on appellant to show some unobvious or unexpected beneficial properties in his compound in order to establish patentability", *Ex parte Henkel* 130 USPQ 474, (1-phenyl-3-methyl-4-hydroxypyrazole obvious over reference teaching 3-phenyl-5-methyl-4-hydroxypyrazole), "appellants have made no comparative showing here establishing the distinguishing characteristics they allege which we might consider as evidence that the claimed compounds are unobvious. It is clear from *In re Henze*, supra, and the authorities it cites, that at least this much is necessary to establish patentability in adjacent homologs and **position isomers** (emphasis added)".

In re Surrey 138 USPQ 67, (2,6-dimethylphenyl-N-(3-dimethylaminopropyl) carbamate obvious over a reference teaching 2,4-dimethylphenyl N-(3-dimethylaminopropyl) carbamate), *In re MEHTA* 146 USPQ 284, (2-(1-methyl)-pyrrolidylmethyl benzilate obvious over a reference teaching 3-(1-methyl)-pyrrolidylmethyl benzilate), "[t]he fact that a **position isomer** (emphasis added) of a compound is known is some evidence of the obviousness of that compound. **Position isomerism** (emphasis added) is a fact of close *structural* (emphasis in original) similarity ...". *Deutsche Gold-Und Silber-Scheideanstalt Vormals Roessler v. Commissioner of Patents*, 148 USPQ 412, (1-azaphenothiazines obvious over references teaching 2-

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azaphenothiazines, 3-azaphenothiazines, and 4-azaphenothiazines), *In re Crounse*, 150 USPQ 554 (dye with *para* (CONH₂) and *ortho* (OCH₃) obvious over a dye with the same nucleus and *meta* (CONH₂) and *para* (OCH₃) group), *Ex parte Allais*, 152 USPQ 66, (3-β-aminopropyl-6-methoxyindole obvious over a reference teaching 3-β-aminopropyl-5-methoxyindole), *In re Wiechert* 152 USPQ 247, (1-methyl dihydrotestosterones obvious over a reference teaching 2-methyl dihydrotestosterones), *Monsanto Company v. Rohm and Haas Company*, 164 USPQ 556, at 559, (3',4'-dichloropropionanilide obvious over references teaching 2',4'-dichloropropionanilide and 2',5'-dichloropropionanilide), *Ex parte Naito and Nakagawa*, 168 USPQ 437, (3-phenyl-5-alkyl-isothiazole-4-carboxylic acid obvious over a reference teaching 5-phenyl-3-alkyl-isothiazole-4-carboxylic acid), "[t]his merely involves **position isomers** (emphasis added) and under the decisions cited, the examiner's holding of *prima facie* obviousness is warranted." *In re Fouche*, 169 USPQ 429, (10-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene obvious over reference teaching 5-aliphatic substituted derivatives of dibenzo[a,d]cycloheptadiene). *In re Hass* 60 USPQ 552, which found a *prima facie* case of obviousness of 1-chloro-1-nitrobutane over 1-chloro-1-nitroisobutane taught in the prior art, *Ex parte Ullyot*, 103 USPQ 185, which found a *prima facie* case of of 2-oxo-quinolines obvious over prior art a 1-oxo-isoquinoline, *In re FINLEY*, 81 USPQ 383, 2-ethyl hexyl salicylate over octyl salicylate.

Ex parte Engelhardt, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or **ring** (emphasis added) of a biologically active compound, transfer of such groups to other positions in which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound.

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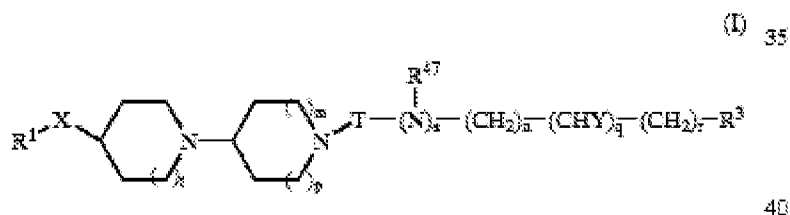
Hence, **position isomerism** (emphasis added) has been used as a tool to obtain new and useful drugs", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or **position isomers** (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-2, 4-6, 9, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10-13 of U.S. patent 6,903,115 in view of Ko et. al. WO 200035877. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '922 patent is drawn to analogs of the generic claims (when Z of the instant claims is tetrazole and Y is a bond). In claim 1 of the '922 application:

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1. A compound of formula (I):



wherein:

- I. q and s are, 0
- II. n and r are, 0,
- III. t, m and p are 1;
- IV. X is O;

VI. T is CH₂;VII. R¹ is phenyl optionally substituted by halogen,VIII. 1 R⁴⁷ hydrogen,IX. R³ is heterocycl,1 R³ are optionally substituted

Since tetrazole is a “heterocycl”, it is clear that the only difference here is the presence of a methylene group in the instant case. See the previous office action 103(a) rejection for the discussion of the obviousness of this modification in the chemokine receptor art.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625